Clinical trial results:
The role of immunosuppressives in immunosenescence and immunotolerance in renal transplantation

Summary

EudraCT number	2011-003604-21
Trial protocol	AT
Global end of trial date	05 April 2013

Results information

Result version number	v1 (current)
This version publication date	17 September 2020
First version publication date	17 September 2020

Trial information

Trial identification

Sponsor protocol code	KT-IBA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 April 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In the present study we investigated the effect of longterm (> 1 year after kidney transplantation) immunosuppressive therapy on T cells from kidney transplanted patients of different age and compared the results to agematched healthy individuals. We also analysed the influence of latent CMV infection on the T cell pool of patients and controls.

Protection of trial subjects:

One blood sample was taken from kidney transplanted patients under immunosuppressive therapy as well as from age-matched healthy controls.

Background therapy:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups. The most commonly used combination of immunosuppressive drugs was tacrolimus with mycophenolate mofetil (MMF) and cortisone (22·1%).

Evidence for comparator:

No comparators were used.

Actual start date of recruitment	18 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	53

From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who underwent a kidney tranplanation at the University Hospital for Internal Medicine IV one or more years ago and who were under immunosuppressive treatment.

Pre-assignment

Screening details:

Indications for transplantation varied greatly among patients. All patients were under immunosuppressive therapy. Patients with symptoms of chronic or acute rejection and patients with impaired transplant function were excluded from the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Young participants

Arm description:

In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.

Arm type	long-term immunosuppressive therapy
Investigational medicinal product name	Certican
Investigational medicinal product code	
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Rapamune
Investigational medicinal product code	
Other name	Sirolismus
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Sandimmun
Investigational medicinal product code	
Other name	Cyclosporin
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Prograf
Investigational medicinal product code	
Other name	Tacrolimus

Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Arm title	Middle-aged participants

Arm description:

In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant
recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.

Arm type	long-term immunosuppressive therapy
Investigational medicinal product name	Certican
Investigational medicinal product code	
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Rapamune
Investigational medicinal product code	
Other name	Sirolismus
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Sandimmun
Investigational medicinal product code	
Other name	Cyclosporin
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Prograf
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Arm title	Elderly participants

Arm description:

In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.

Arm type	long-term immunosuppressive therapy

Investigational medicinal product name	Certican
Investigational medicinal product code	
Other name	Everolimus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Rapamune
Investigational medicinal product code	
Other name	Sirolismus
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Sandimmun
Investigational medicinal product code	
Other name	Cyclosporin
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Investigational medicinal product name	Prograf
Investigational medicinal product code	
Other name	Tacrolimus
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

All patients were under immunosuppressive therapy. Treatment regimens varied among patients, but were similar for the different age groups.

Number of subjects in period 1	Young participants	Middle-aged participants	Elderly participants
Started	21	32	25
Completed	21	32	25

Baseline characteristics

Reporting groups	
Reporting group title	Young participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	
Reporting group title	Middle-aged participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	
Reporting group title	Elderly participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	

Reporting group values	Young participants	Middle-aged participants	Elderly participants
Number of subjects	21	32	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	32	0
From 65-84 years	0	0	25
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	8	12
Male	16	24	13

Reporting group values	Total		
Number of subjects	78		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	53		
From 65-84 years	25		
85 years and over	0		
Gender categorical Units: Subjects			
Female	25		
Male	53		

End points

End points reporting groups

Reporting group title	Young participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	
Reporting group title	Middle-aged participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	
Reporting group title	Elderly participants
Reporting group description:	
In this study, T cell function and the composition of the T cell repertoire were analysed in immunosuppressed renal transplant recipients of different age and cytomegalovirus (CMV) status in comparison to age- and CMV-matched controls.	
Subject analysis set title	Healthy controls, young
Subject analysis set type	Full analysis
Subject analysis set description:	
In addition, peripheral blood was obtained from healthy age-matched control patients.	
Subject analysis set title	Healthy controls, middle aged
Subject analysis set type	Full analysis
Subject analysis set description:	
In addition, peripheral blood was obtained from healthy age-matchedcontrol patients.	
Subject analysis set title	Healthy controls, elderly
Subject analysis set type	Full analysis
Subject analysis set description:	
In addition, peripheral blood was obtained from healthy age-matchedcontrol patients.	

Primary: CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point title	CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)
End point description:	
Analysis of CD4+ effector memory (CD45RO+CD28−) cells in subjects without latent cytomegalovirus (CMV) infection	
End point type	Primary
End point timeframe:	
>1 year after kidney transplantation	

End point values	Young participants	Middle-aged participants	Elderly participants	Healthy controls, young
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	4	27
Units: Percentage				
arithmetic mean (standard error)	2.5 (± 1.7)	5.4 (± 1.2)	7.0 (± 5.4)	0.5 (± 0.1)

End point values	Healthy controls, middle aged	Healthy controls, elderly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	19		
Units: Percentage				
arithmetic mean (standard error)	0.6 (± 0.3)	0.6 (± 0.1)		

Statistical analyses

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV negative, young
Comparison groups	Young participants v Healthy controls, young
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041
Method	t-test, 2-sided

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV negative, middle
Comparison groups	Middle-aged participants v Healthy controls, middle aged
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013
Method	t-test, 2-sided

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV negative, elderly
Comparison groups	Elderly participants v Healthy controls, elderly
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	t-test, 2-sided

Primary: CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point title	CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point description:

Analysis of CD4+ effector memory (CD45RO+CD28−) cells in subjects with latent cytomegalovirus (CMV) infection

End point type	Primary

End point timeframe:

>1 year after kidney transplantation

End point values	Young participants	Middle-aged participants	Elderly participants	Healthy controls, young
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	9	14	12
Units: Percentage				
arithmetic mean (standard error)	4.9 (± 1.8)	5.9 (± 1.7)	9.3 (± 1.9)	3.5 (± 1.2)

End point values	Healthy controls, middle aged	Healthy controls, elderly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	22		
Units: Percentage				
arithmetic mean (standard error)	3.8 (± 1.4)	5.3 (± 0.9)		

Statistical analyses

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV positive, young
Comparison groups	Young participants v Healthy controls, young
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.505
Method	t-test, 2-sided

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV positive, middle
Comparison groups	Middle-aged participants v Healthy controls, middle aged
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38
Method	t-test, 2-sided

Statistical analysis title	CD45RO+CD28− in HC and KTx, CMV positive, elderly
Comparison groups	Elderly participants v Healthy controls, elderly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	t-test, 2-sided

Primary: CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point title	CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point description:

Analysis of CD4+ effector memory (CD45RO−CD28−) cells in subjects without latent cytomegalovirus (CMV) infection

End point type	Primary

End point timeframe:

>1 year after kidney transplantation

End point values	Young participants	Middle-aged participants	Elderly participants	Healthy controls, young
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	8	4	27
Units: Percentage				
arithmetic mean (standard error)	5.4 (± 1.3)	12.5 (± 2.6)	10.0 (± 2.7)	0.9 (± 0.2)

End point values	Healthy controls, middle aged	Healthy controls, elderly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	19		
Units: Percentage				
arithmetic mean (standard error)	2.7 (± 1.4)	0.7 (± 0.1)		

Statistical analyses

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV negative, young
Comparison groups	Young participants v Healthy controls, young

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV negative, middle
Comparison groups	Middle-aged participants v Healthy controls, middle aged
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023
Method	t-test, 2-sided

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV negative, elderly
Comparison groups	Elderly participants v Healthy controls, elderly
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Primary: CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point title	CD4+ T cell subsets in healthy controls (HC) and kidney transplanted immunosuppressed patients (KTx)

End point description:

Analysis of CD4+ effector memory (CD45RO−CD28−) cells in subjects with latent cytomegalovirus (CMV) infection

End point type	Primary

End point timeframe:

>1 year after kidney transplantation

End point values	Young participants	Middle-aged participants	Elderly participants	Healthy controls, young
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	9	14	12
Units: Percentage				
arithmetic mean (standard error)	8.1 (± 2.9)	12.3 (± 3.7)	18.8 (± 3.9)	2.6 (± 1.2)

End point values	Healthy controls, middle aged	Healthy controls, elderly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	22		
Units: Percentage				
arithmetic mean (standard error)	6.5 (± 1.5)	5.7 (± 1.1)		

Statistical analyses

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV positive, young
Comparison groups	Young participants v Healthy controls, young
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064
Method	t-test, 2-sided

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV positive, middle
Comparison groups	Middle-aged participants v Healthy controls, middle aged
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.223
Method	t-test, 2-sided

Statistical analysis title	CD45RO-CD28− in HC and KTx, CMV positive, elderly
Comparison groups	Elderly participants v Healthy controls, elderly
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Proliferation index of T cells	
End point title	Proliferation index of T cells

End point description:

Proliferation index of T cells from healthy subjects (HC) and kidney transplanted patients (KTx)stimulated with anti-CD3 (3 ng/ml) and cultured in medium containing 10 % fetal calf serum (FCS)

days. Proliferation was assessed by carboxyfluorescein succinimidyl ester (CFSE) staining and is expressed as proliferation index.

End point type	Secondary

End point timeframe:

>1 year after kidney transplantation

End point values	Young participants	Middle-aged participants	Elderly participants	Healthy controls, young
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13	13	20	16
Units: proliferation index				
arithmetic mean (standard error)	51.9 (± 5.6)	65.5 (± 4.8)	58.0 (± 3.4)	61.0 (± 3.7)

End point values	Healthy controls, middle aged	Healthy controls, elderly		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	17		
Units: proliferation index				
arithmetic mean (standard error)	60.1 (± 0.0)	64.4 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 18.11.2011- 05.04.2013	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Frequency threshold for reporting non-serious adverse events: 5 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As there were no interventions in this trial, no AEs or SAEs were observed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24028181